(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 December 2001 (13.12.2001)

PCT

(10) International Publication Number
WO 01/94338 A1

(51) International Patent Classification[7]: C07D 401/04, 401/12, 213/81, 213/72, A61K 31/4427, 31/496, 31/551, A61P 29/00

(21) International Application Number: PCT/SE01/01257

(22) International Filing Date: 1 June 2001 (01.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0013737.2 7 June 2000 (07.06.2000) GB

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ALCARAZ, Lilian** [FR/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). **FURBER, Mark** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB).

(74) Agent: **ASTRAZENECA AB**; Global Intellectual Property, S-151 85 Södertälje (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

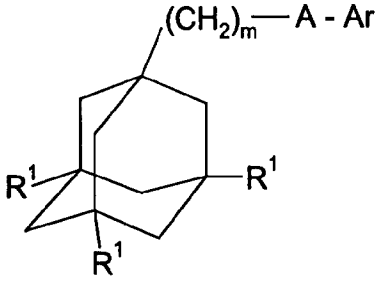
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ADMANTANE DERIVATIVES



(I)

(57) Abstract: The invention provides compounds of general formula (I) in which m, A, R^1 and Ar have the meanings defined in the specification; a process for their preparation; pharmaceutical compositions containing them; a process for preparing the pharmaceutical compositions; and their use in therapy.

WO 01/94338 A1

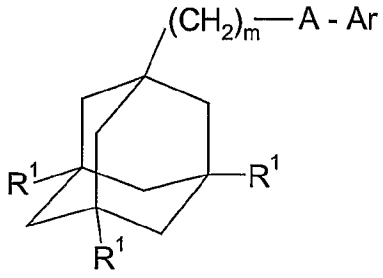
ADMANTANE DERIVATIVES

The present invention relates to adamantane derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

The $P2X_7$ receptor (previously known as P2Z receptor), which is a ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the $P2X_7$ receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1β (IL-1β) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and proliferation (T cells), apoptosis and L-selectin shedding (lymphocytes). $P2X_7$ receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells), hepatocytes and mesangial cells.

It would be desirable to make compounds effective as $P2X_7$ receptor antagonists for use in the treatment of inflammatory, immune or cardiovascular diseases, in the aetiologies of which the $P2X_7$ receptor may play a role.

In accordance with the present invention, there is therefore provided a compound of general formula



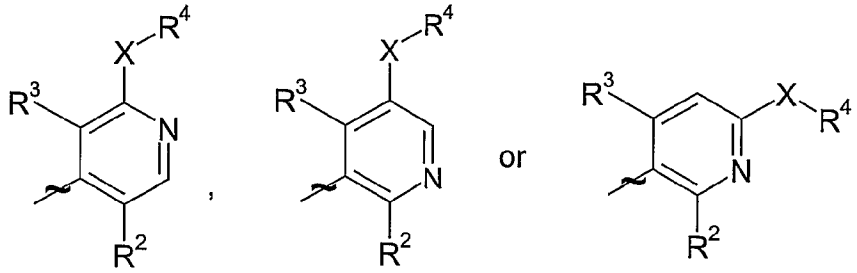
(I)

wherein m represents 1, 2 or 3, preferably 1 or 2;

each R^1 independently represents a hydrogen or halogen (e.g. fluorine, chlorine, bromine or iodine) atom, preferably a hydrogen atom;

A represents C(O)NH or, preferably, NHC(O);

Ar represents a group



;

X represents a bond, an oxygen atom or a group $(CH_2)_{1-6}$, CH=, $(CH_2)_{1-6}O$, $O(CH_2)_{1-6}$, $O(CH_2)_{2-6}O$, $O(CH_2)_{2-3}O(CH_2)_{1-3}$, $(CH_2)_{1-3}O(CH_2)_{1-3}$, $(CH_2)_{1-3}O(CH_2)_{2-3}O$, NR^5, $(CH_2)_{1-6}NR^5$, $NR^5(CH_2)_{1-6}$, $(CH_2)_{1-3}NR^5(CH_2)_{1-3}$, $O(CH_2)_{2-6}NR^5$, $O(CH_2)_{2-3}NR^5(CH_2)_{1-3}$, $(CH_2)_{1-3}NR^5(CH_2)_{2-3}O$, $NR^5(CH_2)_{2-6}O$, $NR^5(CH_2)_{2-3}O(CH_2)_{1-3}$;

one of R^2 and R^3 represents a halogen, cyano, nitro, amino, hydroxyl, or a group selected from (i) C_1-C_6 alkyl optionally substituted by at least one C_3-C_6 cycloalkyl, (ii) C_3-C_8 cycloalkyl, (iii) C_1-C_6 alkyloxy optionally substituted by at least one C_3-C_6 cycloalkyl, and (iv) C_3-C_8 cycloalkyloxy, each of these groups being optionally substituted by one or more fluorine atoms, and the other of R^2 and R^3 represents a hydrogen or halogen atom;

either R^4 represents a 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system containing one or two nitrogen atoms and optionally an oxygen atom, the heterocyclic ring system being optionally substituted by one or more substituents independently selected from fluorine atoms, hydroxyl, carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, $-NR^6R^7$, $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$,

or R^4 represents a 3- to 8-membered saturated carbocyclic ring system substituted by one or more substituents independently selected from $-NR^6R^7$, $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$, the ring system being optionally further substituted by one or more substituents independently selected from fluorine atoms, hydroxyl and C_1-C_6 alkyl;

r is 1, 2, 3, 4, 5 or 6;

R^5 represents a hydrogen atom or a C_1-C_6 alkyl or C_3-C_8 cycloalkyl group;

R^6 and R^7 each independently represent a hydrogen atom or a C_1-C_6 alkyl, C_2-C_6 hydroxyalkyl or C_3-C_8 cycloalkyl group, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring;

with the provisos that,

(a) when A represents C(O)NH and R^4 represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X is other than a bond, and

(b) when A represents C(O)NH and X represents a group $(CH_2)_{1-6}$ or $O(CH_2)_{1-6}$, then R^4 does not represent an unsubstituted imidazolyl, unsubstituted morpholinyl, unsubstituted piperidinyl or unsubstituted pyrrolidinyl group, and

(c) when A represents NHC(O) and R^4 represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X is other than a bond, and

(d) when A represents NHC(O) and X represents $O(CH_2)_{1-6}$ or $NH(CH_2)_{1-6}$, then R^4 does not represent an unsubstituted 1-piperidinyl or unsubstituted 1-pyrrolidinyl group, and

(e) when A represents NHC(O) and X represents $O(CH_2)_{2-3}NH(CH_2)_2$, then R^4 does not represent an imidazolyl group;

or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise indicated, an alkyl substituent or alkyl moiety in a substituent group may be linear or branched. Examples of alkyl groups/moieties containing up to 6 carbon atoms include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl. When one of R^2 and R^3 represents a C_1-C_6 alkyl/C_1-C_6 alkyloxy optionally substituted by at least one C_3-C_6 cycloalkyl, it should be understood that one or both of the alkyl and cycloalkyl moieties may be optionally substituted by fluorine atoms. In relation to R^4, a 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system containing one or two nitrogen atoms and optionally an oxygen atom may be a monocyclic or bicyclic ring system. Also in relation to R^4, a 3- to 8-membered saturated carbocyclic ring system may be a monocyclic or bicyclic ring system. When R^6 or R^7 represents a C_2-C_6 hydroxyalkyl in the substituent

NR^6R^7, $-(CH_2)_rNR^6R^7$ or $-CONR^6R^7$, it will be appreciated that the hydroxyl group will not be bonded to the same carbon atom as the nitrogen atom. When R^6 and R^7 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring, the ring obtained is monocyclic. A hydroxyalkyl substituent may contain one or more hydroxyl groups but preferably contains one hydroxyl group.

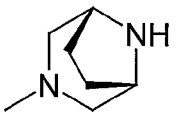
Preferably X represents a bond, an oxygen atom or a group $O(CH_2)_{1-6}$, NR^5 or $NR^5(CH_2)_{1-6}$.

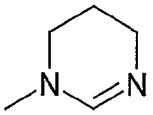
One of R^2 and R^3 represents a halogen (e.g. fluorine, chlorine, bromine or iodine), cyano, nitro, amino, hydroxyl, or a group selected from (i) C_1-C_6 alkyl, preferably C_1-C_4 alkyl, optionally substituted by at least one (e.g. 1, 2 or 3) C_3-C_6 cycloalkyl (i.e. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), (ii) C_3-C_8 cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), (iii) C_1-C_6 alkyloxy, preferably C_1-C_4 alkyloxy, optionally substituted by at least one (e.g. 1, 2 or 3) C_3-C_6 cycloalkyl (i.e. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), and (iv) C_3-C_8 cycloalkyloxy (e.g. cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or cyclohexyloxy), each of these groups being optionally substituted by one or more (e.g. 1, 2, 3 or 4) fluorine atoms, and the other of R^2 and R^3 represents a hydrogen or halogen (e.g. fluorine, chlorine, bromine or iodine) atom.

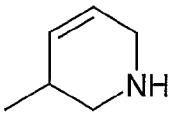
Preferably, one of R^2 and R^3 represents a halogen (especially chlorine) atom and the other of R^2 and R^3 represents a hydrogen atom.

R^4 may represent a 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system containing one or two nitrogen atoms and optionally an oxygen atom, the heterocyclic ring system being optionally substituted by one or more (e.g. 1, 2, 3 or 4) substituents independently selected from fluorine atoms, hydroxyl, carboxyl, cyano, C_1-C_6 alkyl, preferably C_1-C_4 alkyl, C_1-C_6 hydroxyalkyl, preferably C_1-C_4 hydroxyalkyl, $-NR^6R^7$, $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$.

The 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system in the group R^4 may be a monocyclic ring system such as pyrrolidinyl (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl or 3-pyrrolidinyl), piperidinyl (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl or 4-piperidinyl), 4-piperiden-3-yl, piperazinyl (e.g. 1-piperazinyl), homopiperazinyl,

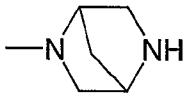


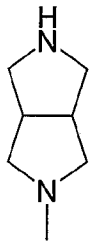
,


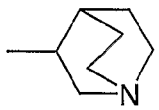
or


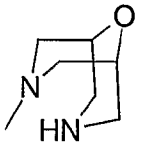
,

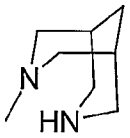
or a bicyclic ring system such as



,


,


,


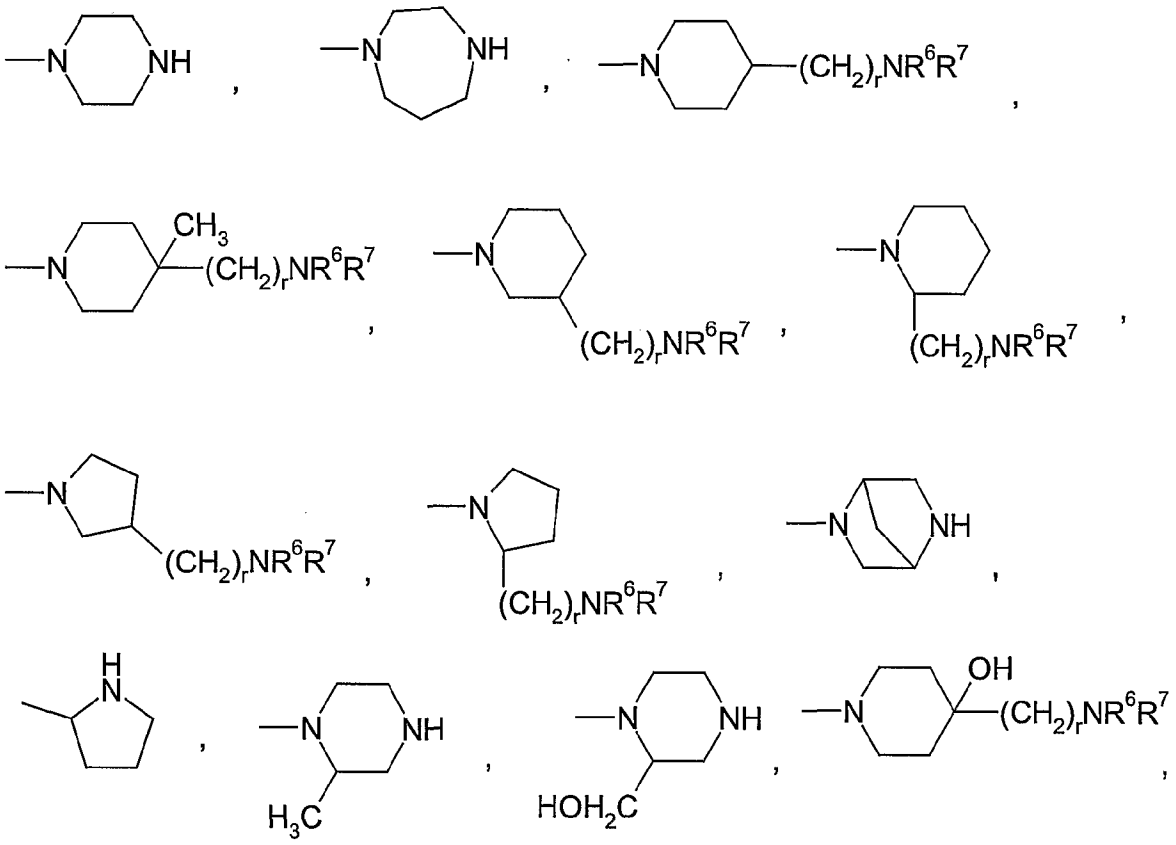
or


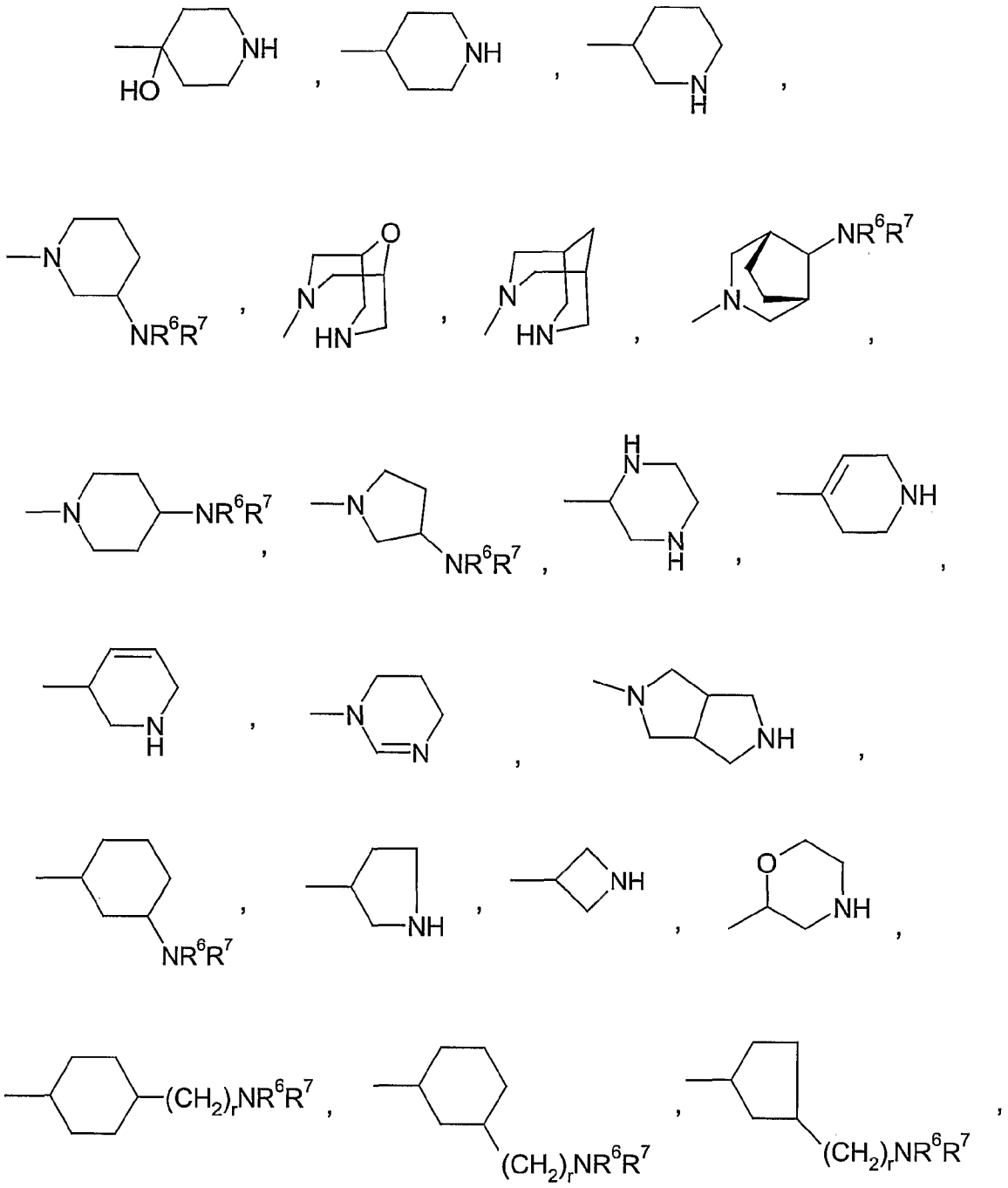
.

Alternatively, R^4 may represent a 3- to 8-membered saturated carbocyclic ring system substituted by one or more (e.g. 1, 2 or 3) substituents independently selected from NR^6R^7, $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$, the ring system being optionally further substituted by one or more (e.g. 1, 2, 3 or 4) substituents independently selected from fluorine atoms, hydroxyl and C_1-C_6 alkyl, preferably C_1-C_4 alkyl.

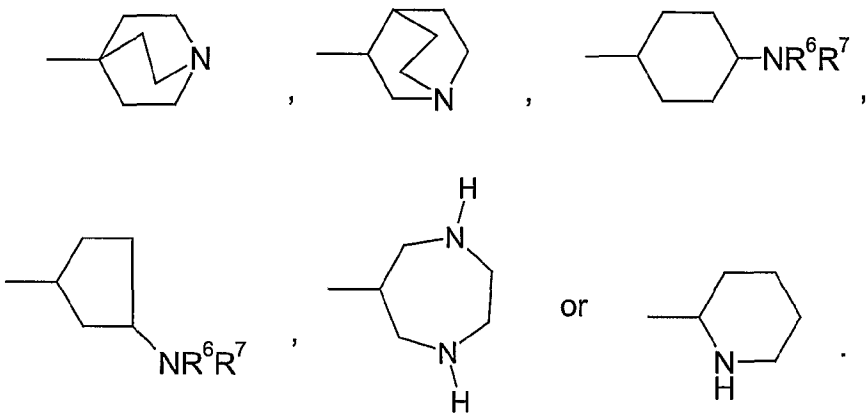
The 3- to 8-membered saturated carbocyclic ring in the group R^4 is preferably a monocyclic ring system such as a cyclopentyl or cyclohexyl ring.

Specific examples of groups R^4 include:

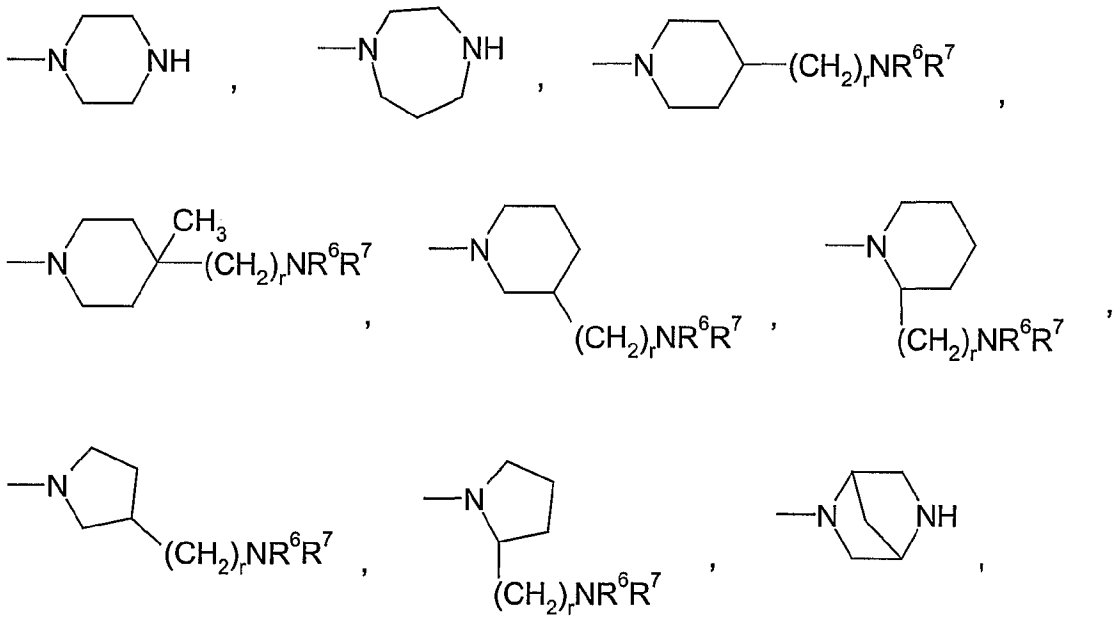


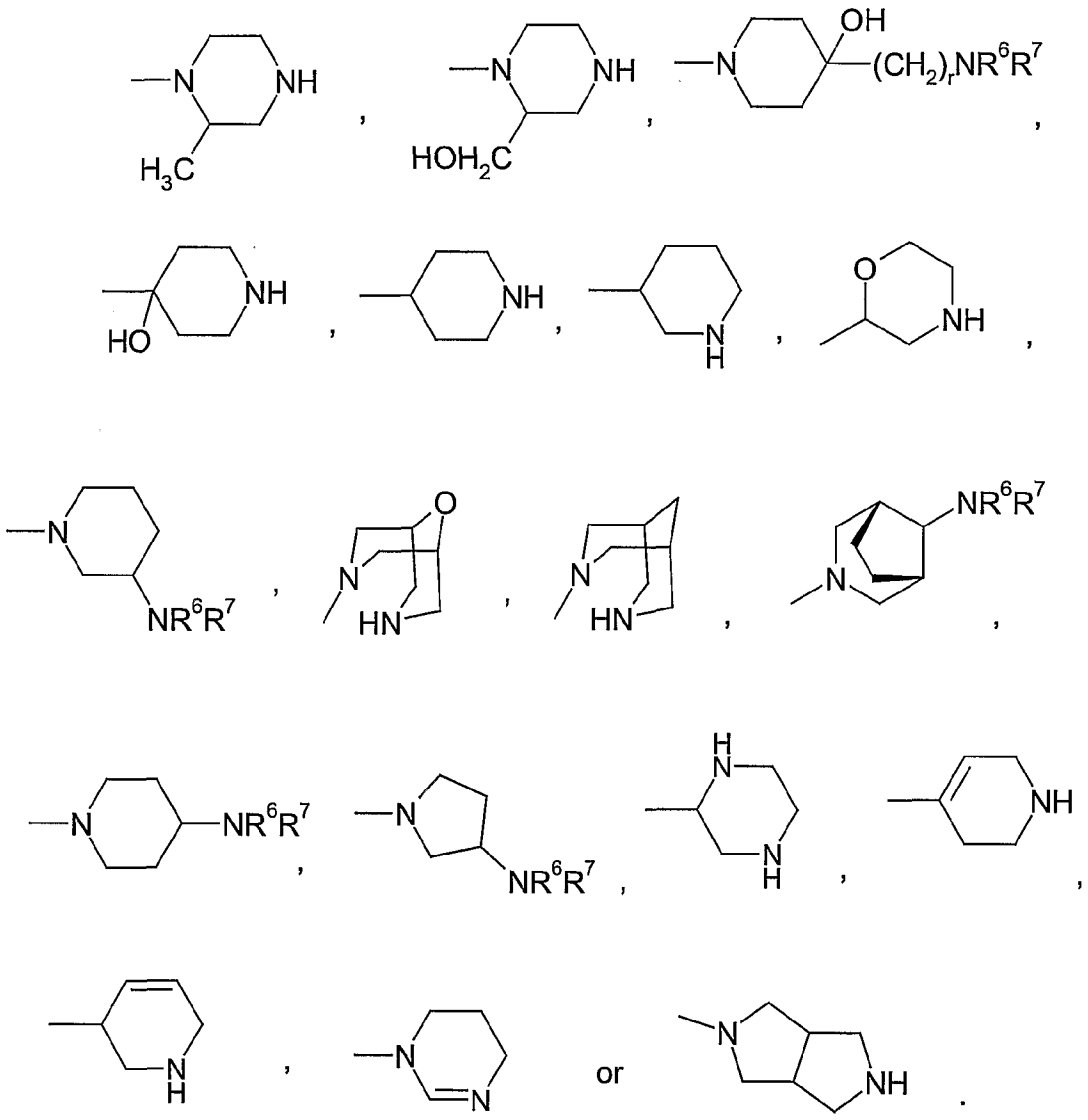


5

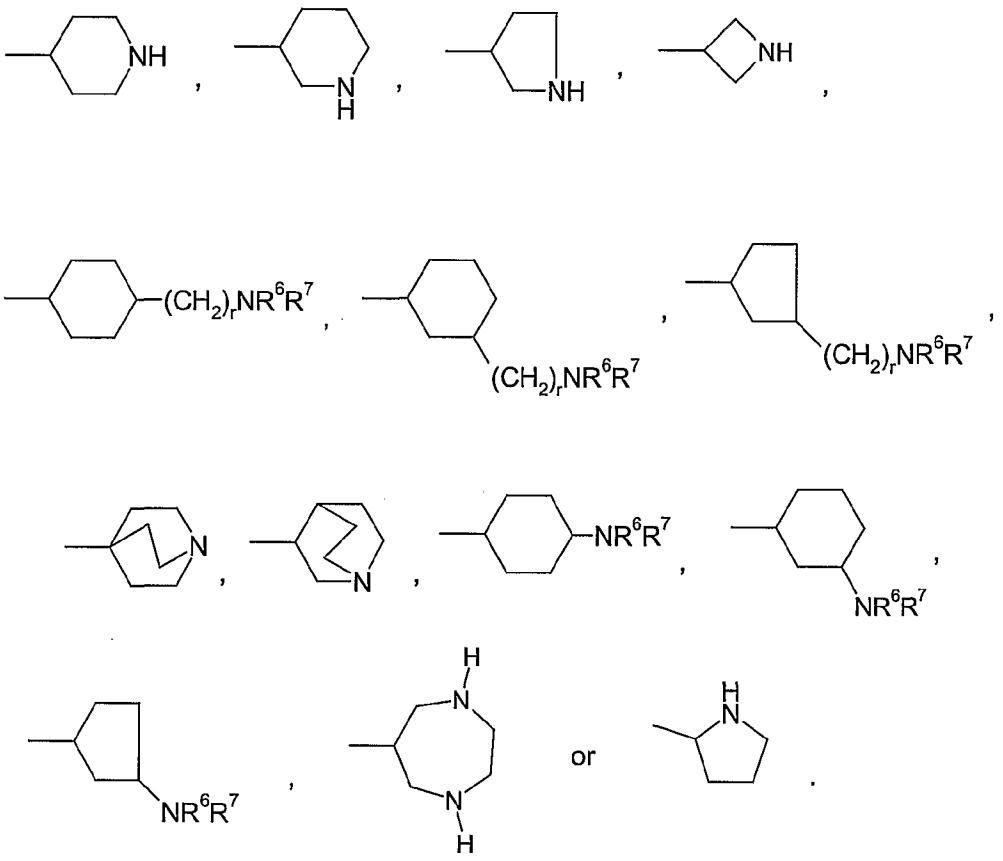


When X represents a bond or a group $(CH_2)_{1-6}$, $O(CH_2)_{2-6}$, $O(CH_2)_{2-3}O(CH_2)_{2-3}$, $(CH_2)_{1-3}O(CH_2)_{2-3}$, $NR^5(CH_2)_{2-6}$, $(CH_2)_{1-3}NR^5(CH_2)_{2-3}$, $O(CH_2)_{2-3}NR^5(CH_2)_{2-3}$ or $NR^5(CH_2)_{2-3}O(CH_2)_{2-3}$, R^4 preferably represents a group:





When X represents an oxygen atom or a group CH=, $(CH_2)_{1-6}O$, OCH_2, $O(CH_2)_{2-6}O$, $O(CH_2)_{2-3}OCH_2$, $(CH_2)_{1-3}OCH_2$, $(CH_2)_{1-3}O(CH_2)_{2-3}O$, NR^5, $(CH_2)_{1-6}NR^5$, $O(CH_2)_{2-6}NR^5$, NR^5CH_2, $(CH_2)_{1-3}NR^5CH_2$, $O(CH_2)_{2-3}NR^5CH_2$, $(CH_2)_{1-3}NR^5(CH_2)_{2-3}O$, $NR^5(CH_2)_{2-6}O$ or $NR^5(CH_2)_{2-3}OCH_2$, R^4 preferably represents a group:



R^5 represents a hydrogen atom, or a C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl) or C_3-C_8, preferably C_3-C_6, cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) group. R^5 is especially a hydrogen atom.

R^6 and R^7 each independently represent a hydrogen atom, or a C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl), C_2-C_6 hydroxyalkyl (e.g. hydroxymethyl or hydroxyethyl) or C_3-C_8, preferably C_3-C_6, cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) group, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 3- to 8-membered, preferably 3- to 6-membered, saturated heterocyclic ring such as a pyrrolidinyl or piperidinyl ring.

In the substituent -NR^6R^7, it is especially preferred that R^6 and R^7 both represent a hydrogen atom.

Preferred compounds of the invention include:

5-Chloro-2-piperazinyl-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-([1,4]-diazepan-1-yl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(4-amino-piperidin-1-yl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(4-piperidinylmethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(4-piperidinylmethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(3-aminopyrrolidin-1-yl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(4-piperidinylmethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(3-piperidinylmethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

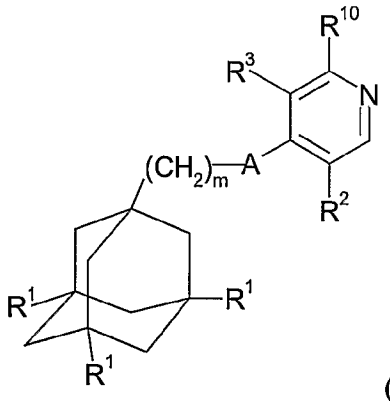
3-Chloro-2-piperazinyl-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

3-Chloro-2-(4-aminopiperidin-1-yl) -*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt, and

3-Chloro-2-(4-piperidinylmethylamino) -*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt.

The present invention further provides a process for the preparation of a compound of formula (I) as defined above which comprises:

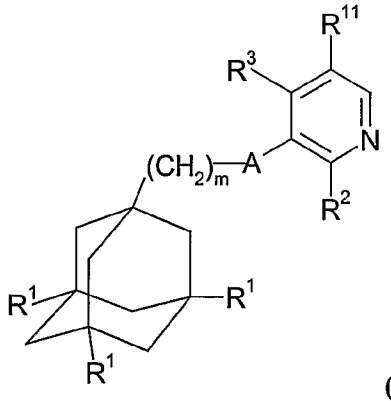
(i) when X represents an oxygen atom or a group $O(CH_2)_{1-6}$, $O(CH_2)_{2-6}O$, $O(CH_2)_{2-3}O(CH_2)_{1-3}$, $O(CH_2)_{2-6}NR^5$ or $O(CH_2)_{2-3}NR^5(CH_2)_{1-3}$, reacting a compound of general formula



(II)

wherein R^{10} represents a leaving group (e.g. a chlorine atom) and m, A, R^1, R^2 and R^3 are as defined in formula (I), or

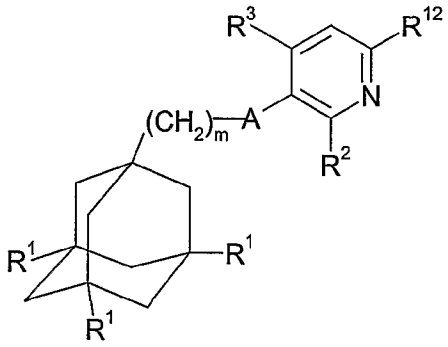
a compound of general formula



(III)

wherein R^{11} represents a leaving group (e.g. a chlorine atom) and m, A, R^1, R^2 and R^3 are as defined in formula (I), or

a compound of general formula



(IV)

wherein R^{12} represents a leaving group (e.g. a chlorine atom) and m, A, R^1, R^2 and R^3 are as defined in formula (I),

with a compound of general formula

$$R^4 - Y - OH \quad (V)$$

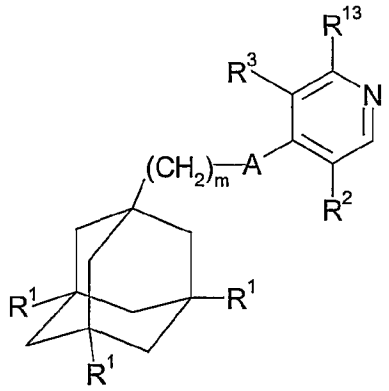
wherein Y represents a bond or a group $(CH_2)_{1-6}$, $O(CH_2)_{2-6}$, $(CH_2)_{1-3}O(CH_2)_{2-3}$, $NR^5(CH_2)_{2-6}$ or $(CH_2)_{1-3}NR^5(CH_2)_{2-3}$ and R^4 is as defined in formula (I), in the presence of a base (e.g. sodium hydride) or in the presence of a combination of a palladium catalyst (e.g. palladium acetate), a phospine ligand (e.g. BINAP) and a base (e.g. cesium carbonate); or

(ii) when X represents a bond or a group NR^5, $NR^5(CH_2)_{1-6}$, $NR^5(CH_2)_{2-6}O$ or $NR^5(CH_2)_{2-3}O(CH_2)_{1-3}$, reacting a compound of formula (II), (III) or (IV) as defined in (i) above, with a compound of general formula

$$R^4 - Z \quad (VI)$$

wherein Z represents a hydrogen atom or a group NHR^5, $(CH_2)_{1-6}NHR^5$, $O(CH_2)_{2-6}NHR^5$ or a group $(CH_2)_{1-3}O(CH_2)_{2-3}NHR^5$ and R^4 and R^5 are as defined in formula (I), optionally in the presence of a palladium catalyst (e.g. palladium acetate), a phosphine ligand (e.g. BINAP) and a base (e.g. cesium carbonate); or

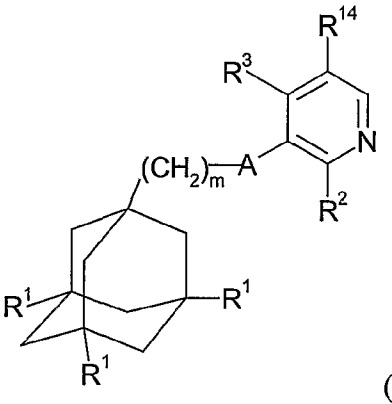
(iii) when X represents a CH_2 group, R^4 represents an optionally substituted 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system as defined in formula (I) and R^4 is linked to X through a nitrogen atom, reacting a compound of general formula



(VII)

wherein R^{13} represents a group $-CH_2L^1$, L^1 represents a leaving group (e.g. a halogen atom) and m, A, R^1, R^2 and R^3 are as defined in formula (I), or

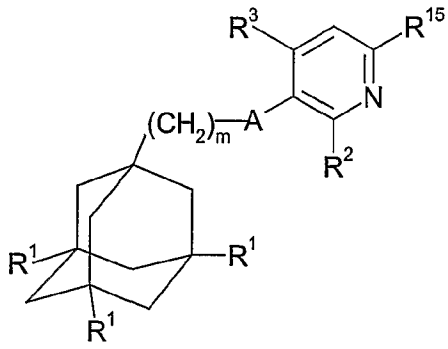
a compound of general formula



(VIII)

wherein R^{14} represents a group $-CH_2L^2$, L^2 represents a leaving group (e.g. a halogen atom) and m, A, R^1, R^2 and R^3 are as defined in formula (I), or

a compound of general formula



(IX)

wherein R^{15} represents a group $-CH_2L^3$, L^3 represents a leaving group (e.g. a halogen atom) and m, A, R^1, R^2 and R^3 are as defined in formula (I),

with a compound of general formula

$$R^{4'} - H \qquad (X)$$

wherein $R^{4'}$ represents an optionally substituted 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system as defined in R^4 in formula (I), in the presence of a base (e.g. diisopropylethylamine); or

(iv) when X represents a group CH_2O, reacting a compound of formula (VII), (VIII) or (IX) as defined in (iii) above with a compound of formula (V) as defined in (i) above wherein Y represents a bond, in the presence of a base (e.g. sodium hydride) or in the presence of a metal salt (e.g. silver trifluoromethanesulfonate); or

(v) when X represents a group CH_2NR^5, reacting a compound of formula (VII), (VIII) or (IX) as defined in (iii) above with a compound of formula (VI) as defined in (ii) above wherein Z represents a group NHR^5; or

(vi) when X represents a group CH=, reacting a compound of formula (VII), (VIII) or (IX) as defined in (iii) above with trimethyl phophite and then with a compound of general formula (XI), $R^4 = O$, wherein R^4 is as defined in formula (I), in the presence of a base (e.g. lithium diisopropylamide); or

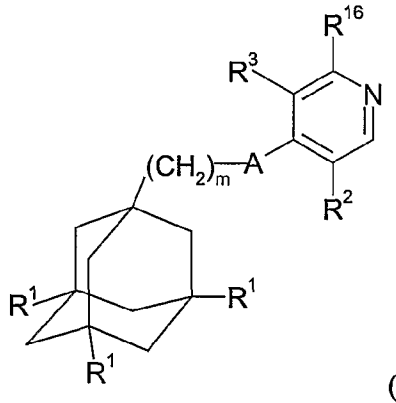
(vii) when X represents a group $(CH_2)_{2-6}$, reacting a compound of formula (VII), (VIII) or (IX) as defined in (iii) above with trimethylphosphite and then with either a compound of general formula (XII), R^4CHO, wherein R^4 is as defined in formula (I) or with a compound of general formula (XIII), $R^4(CH_2)_{1-4}CHO$, in which R^4 is as defined in formula (I), in the presence of a base (e.g. lithium diisopropylamide), followed by a hydrogenation reaction (e.g. using a platinum oxide catalyst); or

(viii) when X represents a group $(CH_2)_{2-6}O$, reacting a compound of formula (VII), (VIII) or (IX) as defined in (iii) above with trimethylphosphite and then with a compound

of general formula (XIV), $R^4O(CH_2)_{1-4}CHO$, in which R^4 is as defined in formula (I), in the presence of a base (e.g. lithium diisopropylamide), followed by a hydrogenation reaction (e.g. using a platinum oxide catalyst); or

(ix) when X represents a group $(CH_2)_{2-6}NR^5$, reacting a compound of formula (VII), (VIII) or (IX) as defined in (iii) above with trimethylphosphite and then with a compound of general formula (XV), $R^4NR^5(CH_2)_{1-4}CHO$, in which R^4 and R^5 are as defined in formula (I), in the presence of a base (e.g. lithium diisopropylamide), followed by a hydrogenation reaction (e.g. using a platinum oxide catalyst); or

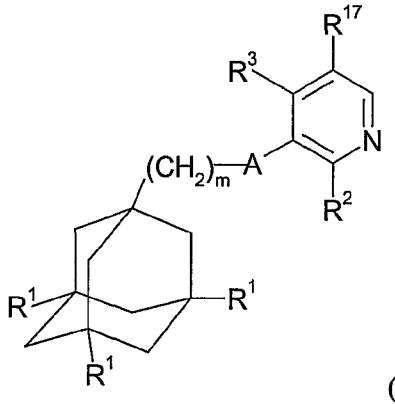
(x) when X represents a group $(CH_2)_{1-3}O(CH_2)_{1-3}$ or $(CH_2)_{1-3}O(CH_2)_{2-3}O$, reacting a compound of general formula



(XVI)

wherein R^{16} represents a group $-(CH_2)_{1-3}L^4$, L^4 represents a leaving group (e.g. methanesulphonate or p-toluenesulphonate) and m, A, R^1, R^2 and R^3 are as defined in formula (I), or

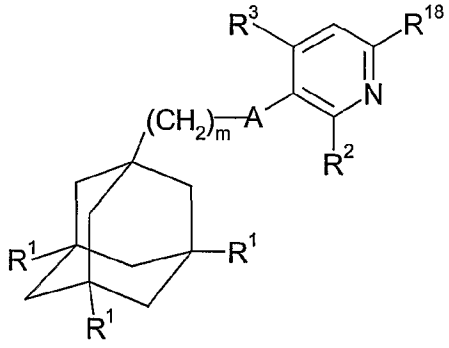
a compound of general formula



(XVII)

wherein R^{17} represents a group $-(CH_2)_{1-3}L^5$, L^5 represents a leaving group (e.g. methanesulphonate or p-toluenesulphonate) and m, A, R^1, R^2 and R^3 are as defined in formula (I), or

a compound of general formula



(XVIII)

wherein R^{18} represents a group $-(CH_2)_{1-3}L^6$, L^6 represents a leaving group (e.g. methanesulphonate or p-toluenesulphonate) and m, A, R^1, R^2 and R^3 are as defined in formula (I),

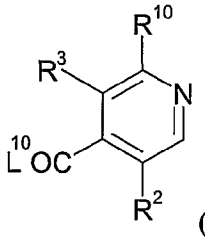
with a compound of formula (V) as defined in (i) above wherein Y represents a group $(CH_2)_{1-3}$ or $O(CH_2)_{2-3}$, in the presence of a base (e.g. sodium hydride); or

(xi) when X represents a group $(CH_2)_{1-3}NR^5(CH_2)_{1-3}$ or $(CH_2)_{1-3}NR^5(CH_2)_{2-3}O$ reacting a compound of formula (XVI), (XVII) or (XVIII) as defined in (x) above with a compound of formula (VI) as defined in (ii) above wherein Z represents a group $(CH_2)_{1-3}NHR^5$ or $O(CH_2)_{2-3}NHR^5$;

and optionally after (i), (ii), (iii), (iv), (v), (vi), (vii), (viii), (ix), (x) or (xi) converting the compound of formula (I) to a further compound of formula (I) and, if desired, forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

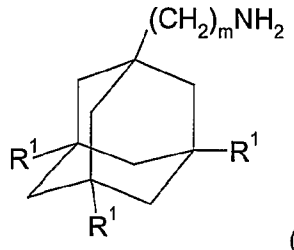
The processes of the invention may conveniently be carried out in a solvent, e.g. an organic solvent such as dichloromethane, dichloroethane, tetrahydrofuran, dioxane, xylene or dimethylformamide, at a temperature, e.g. in the range from 0 to 200 °C, preferably in the range from 0 to 150 °C.

Compounds of formula (II) in which A is NHC(O) may be prepared by reacting a compound of general formula



(XXX)

wherein L^{10} represents a leaving group (e.g. a hydroxyl or chloride leaving group) and R^2, R^3 and R^{10} are as defined in formula (II), with a compound of general formula

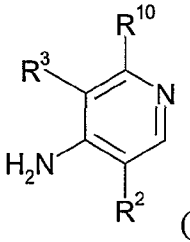


(XXXI)

wherein m and R^1 are as defined in formula (I), optionally in the presence of a coupling agent (e.g. 1,1'-carbonyldiimidazole).

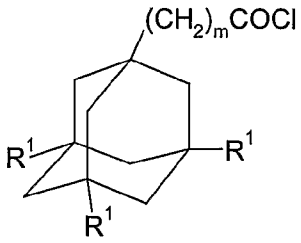
Compounds of formulae (III), (IV), (VII), (VIII), (IX), (XVI), (XVII) and (XVIII) in which A is NHC(O) may be prepared in a similar manner to the compounds of formula (II).

Compounds of formula (II) in which A is C(O)NH may be prepared by reacting a compound of general formula



(XXXII)

wherein R^2, R^3 and R^{10} are as defined in formula (II), with a compound of general formula



(XXXIII)

wherein m and R^1 are as defined in formula (I), optionally in the presence of a base (e.g. diisopropylethylamine).

Compounds of formulae (III), (IV), (VII), (VIII), (IX), (XVI), (XVII) and (XVIII) in which A is C(O)NH may be prepared in a similar manner to the compounds of formula (II).

Compounds of formulae (V), (VI), (X), (XI), (XII), (XIII), (XIV), (XV), (XXX), (XXXI), (XXXII) and (XXXIII) are either commercially available, are well known in the literature or may be prepared easily using known techniques.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures. For example, compounds of formula (I) in which one of R^2 and R^3 represents a nitro group can be converted to compounds of formula (I) in which one of R^2 and R^3 represents an amino group by reduction using iron powder and ammonium chloride in ethanol/water under reflux conditions. The latter compounds can in turn be converted into compounds of formula (I) in which one of R^2 and R^3 represents a halogen atom, e.g. chlorine, by diazotization (e.g. with sodium nitrite) and reaction with copper

chloride. Compounds of formula (I) in which R^6 or R^7 represents a hydrogen atom can be converted to compounds of formula (I) in which R^6 or R^7 represents a C_1-C_6 alkyl, C_2-C_6 hydroxyalkyl, C_3-C_8 cycloalkyl or a 3- to 8-membered saturated heterocyclic ring by standard chemical procedures.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compounds of the present invention are advantageous in that they possess pharmacological activity. They are therefore indicated as pharmaceuticals for use in the treatment of rheumatoid arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma,

chronic obstructive pulmonary disease (COPD), hyperresponsiveness of the airway, septic shock, glomerulonephritis, irritable bowel disease, Crohn's disease, ulcerative colitis, atherosclerosis, growth and metastases of malignant cells, myoblastic leukaemia, diabetes, Alzheimer's disease, meningitis, osteoporosis, burn injury, ischaemic heart disease, stroke and varicose veins.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention further provides a method of effecting immunosuppression (e.g. in the treatment of rheumatoid arthritis, irritable bowel disease, atherosclerosis or psoriasis) which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

The invention also provides a method of treating an obstructive airways disease (e.g. asthma or COPD) which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I)/salt/solvate (active ingredient) may be in the range from 0.001 mg/kg to 30 mg/kg.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

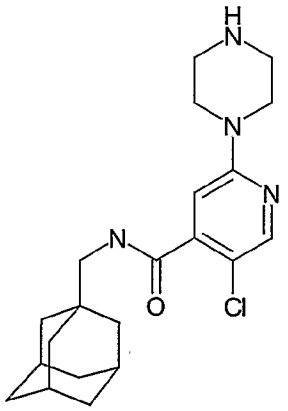
The pharmaceutical composition of the invention may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by

parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The present invention will now be further explained by reference to the following illustrative examples.

Example 1

5-Chloro-2-piperazinyl-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt



a) 2,5-Dichloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide

To a stirred suspension of 2,5-dichlorpyridine-4-carboxylic acid (1.53g, WO 96/33975) in dichloromethane (20ml) and dimethylformamide (0.02ml) at room temperature was added portionwise oxalyl chloride (3ml). Once complete solution was achieved the mixture was stirred for a further 1 hour then concentrated in vacuo. The compound was redissolved in dichloromethane and added slowly to a solution of adamantylmethylamine in dichloromethane (20ml) and diisopropylethylamine (2ml). The mixture was partitioned between saturated aqueous sodium bicarbonate solution and dichloromethane and the organic layer dried over magnesium sulphate. Concentration in vacuo and crystallization (diethyl ether: isohexane) gave the sub-title compound as colourless crystals (1.62g).

MS (APCI +ve) 339.1038 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.59 (1H, t); 8.58 (1H, s); 7.65 (1H, s); 2.94 (2H, d); 1.94 (3H, bs); 1.7-1.57 (6H, m); 1.51 (6H, s).

b) 5-Chloro-2-piperazinyl-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt

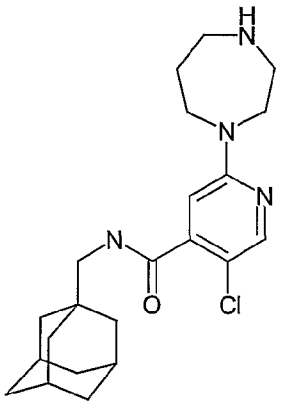
A solution of 2,5-dichloro-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide (0.30g, Example 1a) and 1-*t*-butoxycarbonylpiperazine (0.344g) in dimethylsulfoxide (3ml) was heated at 160°C for 40min. The solution was cooled and partitioned between saturated aqueous sodium bicarbonate solution and dichloromethane and the organic layer dried over magnesium sulphate. Concentration in vacuo and chromatography on silica gave a colourless solid. This was redissolved in methanol and treated with 4M HCl in dioxan (4ml). Once deprotection was complete the solution was partially concentrated in vacuo then diluted slowly with diethyl ether with rapid stirring. The resulting white precipitate was filtered, washed with diethyl ether and dried to afford the title compound (0.195g).

MS (APCI +ve) 389.2110 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 9.43 (2H, s); 8.43 (1H, t); 8.20 (1H, s); 6.93 (1H, s); 3.77 (4H, m); 3.13 (4H, s, br); 2.93 (2H, d); 1.94 (3H, bs); 1.75-1.55 (6H, m); 1.52 (6H, s).

Example 2

5-Chloro-2-([1,4]-diazepan-1-yl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt



A solution of 2,5-dichloro-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide (0.50g, Example 1a) and 1-*t*-butoxycarbonylhomopiperazine (0.76g) in dimethylsulfoxide (5ml) was heated at 100-120°C for 24 hours. The solution was cooled and partitioned between saturated aqueous sodium bicarbonate solution and dichloromethane and the organic layer dried over magnesium sulphate. Concentration in vacuo and chromatography on silica gave a colourless solid. This was redissolved in methanol (10ml) and treated with 4M HCl in dioxan (2ml). Once deprotection was complete (14 hours) the solution was partially concentrated in vacuo then diluted slowly with diethyl ether with rapid stirring. The resulting white precipitate was filtered, washed with diethyl ether and dried to afford the title compound (0.51g).

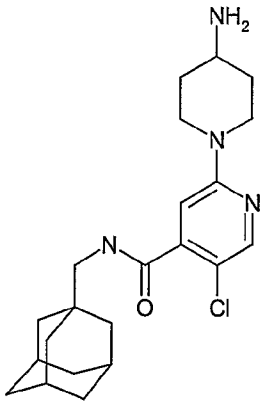
MS (APCI +ve) 403.2256 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 9.23 (2H, s); 8.40 (1H, t); 8.14 (1H, s); 6.72 (1H, s); 3.92 (2H, m); 3.67 (2H, t); 3.19 (2H, m); 3.10 (2H, m); 2.93 (2H, d); 2.09 (2H, m); 1.94 (3H, m); 1.75-1.5 (6H, m); 1.52 (6H, s).

Following the procedure described in Example 1b and Example 2 the following compounds were prepared:

Example 3

5-Chloro-2-(4-amino-piperidin-1-yl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt

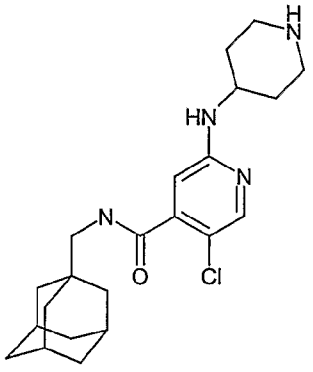


MS (APCI +ve) 403.2256 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 9.23 (2H, s); 8.40 (1H, t); 8.14 (1H, s); 6.72 (1H, s); 3.92 (2H, m); 3.67 (2H, t); 3.19 (2H, m); 3.10 (2H, m); 2.93 (2H, d); 2.09 (2H, m); 1.94 (3H, m); 1.75-1.5 (6H, m); 1.52 (6H, s).

Example 4

5-Chloro-2-(4-piperidinylmethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt

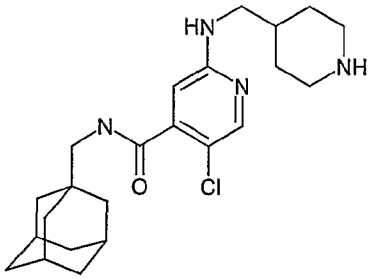


MS (APCI +ve) 403.2256 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 9.23 (2H, s); 8.40 (1H, t); 8.14 (1H, s); 6.72 (1H, s); 3.92 (2H, m); 3.67 (2H, t); 3.19 (2H, m); 3.10 (2H, m); 2.93 (2H, d); 2.09 (2H, m); 1.94 (3H, m); 1.75-1.5 (6H, m); 1.52 (6H, s).

Example 5

5-Chloro-2-(4-piperidinylmethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt

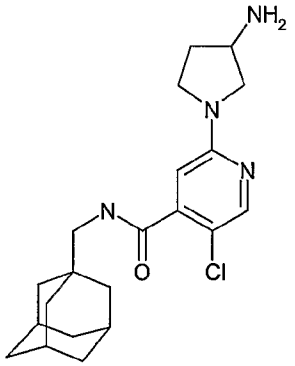


MS (APCI +ve) 417.2423 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.82 (1H, m); 8.54 (1H, m); 8.42 (1H, t); 8.01 (1H, s); 6.59 (1H, s); 3.27-3.17 (4H, m); 2.90 (2H, d); 2.81 (2H, m); 1.94 (3H, m); 1.83 (3H ,m); 1.70-1.5 (6H, m); 1.50 (6H, s); 1.34 (2H, m).

Example 6

5-Chloro-2-(3-aminopyrrolidin-1-yl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt

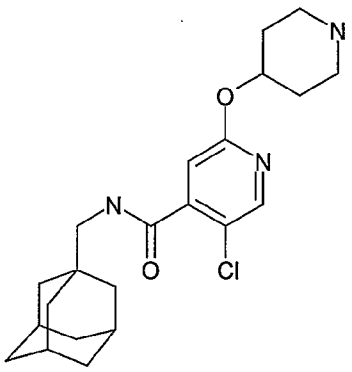


MS (APCI +ve) 438.2120 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.43 (1H, t); 8.38 (3H, s, br); 8.14 (1H, s); 6.50 (1H, s); 3.92 (1H, m); 3.67 (1H, dd); 3.63-3.5 (2H, m); 3.46 (1H, m); 2.92 (2H, m); 2.32 (1H, m); 2.12 (1H, m); 1.94 (3H, s, br); 1.70-1.55 (6H, m); 1.50 (6H, s).

Example 7

5-Chloro-2-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt



A solution of 2,5-dichloro-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide (0.30g, Example 1a) and 1-*t*-butoxycarbonylpiperidine-4-ol (0.344g) in anhydrous tetrahydrofuran (10ml) was heated with sodium hydride (50mg, 60% dispersion) at 70°C for 24 hours. The solution was cooled, glacial acetic acid (0.1ml) was added and the mixture partitioned between saturated aqueous sodium bicarbonate solution

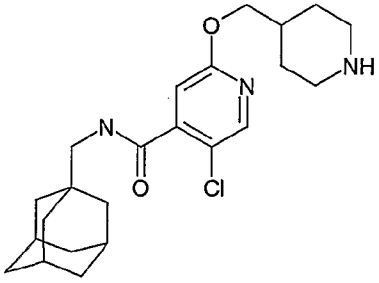
and dichloromethane. The organic layer was dried over magnesium sulphate, concentrated in vacuo and chromatographed on silica (ethyl acetate: isohexane) to give a colourless solid. This was redissolved in methanol (20ml) and treated with 4M HCl in dioxan (4ml). Once deprotection was complete (14 hours) the solution was partially concentrated in vacuo then diluted slowly with diethyl ether with rapid stirring. The resulting white precipitate was filtered, washed with diethyl ether and dried to afford the title compound (0.090g).

^{1}H NMR (DMSO-d_6) δ 9.06 (2H, s, br); 8.50 (1H, t); 8.265 (1H, s); 6.88 (1H, s); 5.22 (1H, m); 3.17 (2H, m); 3.10 (2H, m); 2.93 (2H, d); 2.14 (2H, m); 1.94 (5H, m); 1.7-1.55 (6H, m); 1.55 (6H, s).

Following the procedure described in Example 7 the following compounds were prepared:

Example 8

5-Chloro-2-(4-piperidinylmethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt

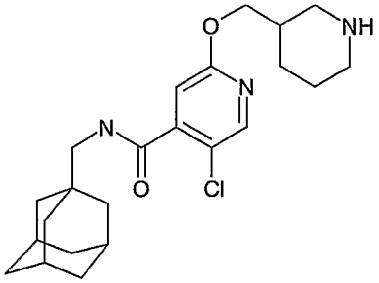


MS (APCI +ve) 418.2261 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.92 (1H, m); 8.62 (1H, m); 8.50 (1H, t); 8.26 (1H, s); 6.83 (1H, s); 4.16 (2H, m + H_2O); 3.27 (2H, d); 2.90 (2H, d); 2.85 (2H, m); 2.07 (1H, m); 1.94 (3H, m); 1.88 (2H, d); 1.75-1.55 (6H, m); 1.58 (6H, s); 1.55-1.40 (1-2H, m).

Example 9

5-Chloro-2-(3-piperidinylmethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt

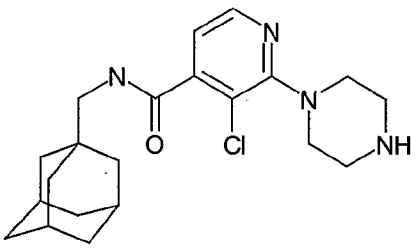


MS (APCI +ve) 418.2261 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 9.03 (1H, m); 8.86 (1H, t); 8.51 (1H, t); 8.26 (1H, s, br); 6.87 (1H, s); 4.3-4.0 (2H, m + H_2O); 3.31 (1H, d); 3.22 (1H, d); 2.93 (2H, d); 2.75 (2H, m); 2.25 (1H, m); 1.94 (3H, s, br); 1.81 (2H, d); 1.70-1.58 (7H, m); 1.51 (6H, s); 1.33 (1H, m).

Example 10

3-Chloro-2-piperazinyl-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt



a) 2,3-Dichloro-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide

To a stirred suspension of 2,3-dichlorpyridine-4-carboxylic acid (2.1g, WO 96/33975) in dichloromethane (100ml) and dimethylformamide (0.03ml) at room temperature was added portionwise oxalyl chloride (2ml). The mixture was stirred for a further 4 hours then concentrated in vacuo. The compound was redissolved in dichloromethane and added slowly to a solution of adamantylmethylamine (2g) in dichloromethane (20ml) and diisopropylethylamine (3ml) at 0°C. The mixture was

partitioned between saturated aqueous sodium bicarbonate solution and dichloromethane and the organic layer dried over magnesium sulphate. Concentration in vacuo and chromatographed on silica (ethyl acetate: isohexane) gave the sub-title compound (1.28g).

^{1}H NMR (DMSO-d_6) δ 8.59 (1H, t); 8.43 (1H, d); 7.48 (1H, d); 2.95 (2H, d); 1.99 (3H, bs); 1.7-1.6 (6H, m); 1.51 (6H, s).

b) 3-Chloro-2-piperazinyl-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt

A solution of 2,3-dichloro-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide (0.15g, Example 10a) and 1-*t*-butoxycarbonylpiperazine (0.19g) in dimethylsulfoxide (2ml) was heated at 100°C for 8 hours. The solution was cooled and partitioned between saturated aqueous sodium bicarbonate solution and dichloromethane and the organic layer dried over magnesium sulphate. Concentration in vacuo and chromatography on silica gave a colourless solid. This was redissolved in methanol and treated with 4M HCl in dioxan (4ml). Once deprotection was complete the solution was partially concentrated in vacuo then diluted slowly with diethyl ether with rapid stirring. The resulting white precipitate was filtered, washed with diethyl ether and dried to afford the title compound (0.050g).

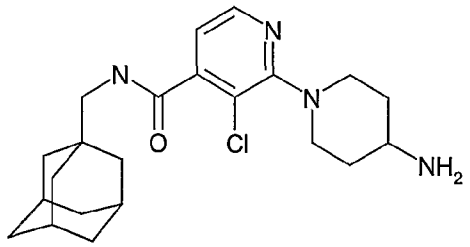
MS (APCI +ve) 389.2122 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 9.32 (2H, s, br); 8.47 (1H, t); 8.28 (1H, d); 7.07 (1H, d); 3.47 (4H, m); 3.22 (4H, s, br); 2.93 (2H, d); 1.94 (3H, s, br); 1.7-1.55 (6H, m); 1.51 (6H, s).

Following the procedure described in Example 10 the following compounds were prepared:

Example 11

3-Chloro-2-(4-aminopiperidin-1-yl) -*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt

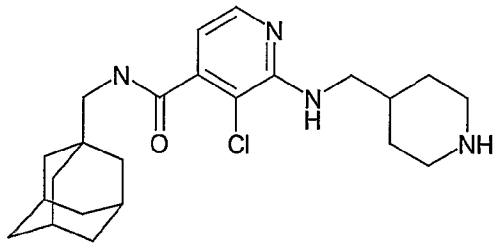


MS (APCI +ve) 403.2268 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.45 (1H, t); 8.22 (1H, s); 8.22 (3H, s, br); 6.97 (1H, d); 3.74 (2H, d, br); 3.21 (1H, m); 2.93 (2H, d); 2.86 (2H, m); 2.02 (2H, d, br); 1.91 (3H, s, br); 1.8-1.55 (8H, m); 1.51 (6H, s).

Example 12

3-Chloro-2-(4-piperidinylmethylamino) -*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt



MS (APCI +ve) 417.2426 $(M+H)^+$

^{1}H NMR (DMSO-d_6) δ 8.90 (1H, d, br); 8.65 (1H, m); 8.42 (1H, t); 7.98 (1H, d); 7.12 (1H, s, br); 6.55 (1H, d); 3.34 (2H, s, br); 3.24 (2H, d); 2.91 (2H, d); 2.79 (2H, m); 1.94 (4H, s, br); 1.80 (2H, d, br); 1.70-1.55 (6H, m); 1.51 (6H, s); 1.37 (2H, m).

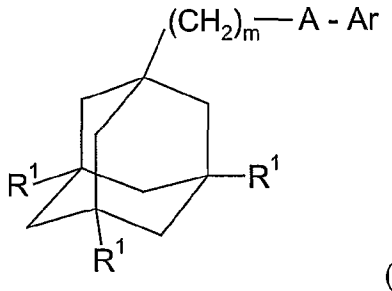
Pharmacological Analysis

Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the $P2X_7$ receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3), p.126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. The increase in fluorescence can be used as a measure of $P2X_7$ receptor activation and therefore to quantify the effect of a compound on the $P2X_7$ receptor.

In this manner, each of the title compounds of Examples 1 to 12 was tested for antagonist activity at the $P2X_7$ receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 250 µl of test solution comprising 200 µl of a suspension of THP-1 cells (2.5×10^6 cells/ml) containing 10^{-4}M ethidium bromide, 25 µl of a high potassium buffer solution containing 10^{-5}M bbATP, and 25 µl of the high potassium buffer solution containing 3×10^{-5}M test compound. The plate was covered with a plastics sheet and incubated at 37 °C for one hour. The plate was then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a $P2X_7$ receptor agonist) and pyridoxal 5-phosphate (a $P2X_7$ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC_{50} figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of Examples 1 to 12 demonstrated antagonist activity, having a pIC_{50} figure > 4.50.

CLAIMS

1. A compound of general formula



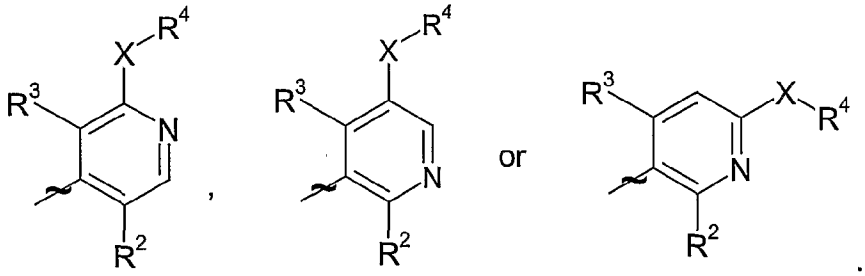
(I)

wherein m represents 1, 2 or 3;

each R^1 independently represents a hydrogen or halogen atom;

A represents C(O)NH or NHC(O);

Ar represents a group



;

X represents a bond, an oxygen atom or a group $(CH_2)_{1-6}$, CH=, $(CH_2)_{1-6}O$, $O(CH_2)_{1-6}$, $O(CH_2)_{2-6}O$, $O(CH_2)_{2-3}O(CH_2)_{1-3}$, $(CH_2)_{1-3}O(CH_2)_{1-3}$, $(CH_2)_{1-3}O(CH_2)_{2-3}O$, NR^5, $(CH_2)_{1-6}NR^5$, $NR^5(CH_2)_{1-6}$, $(CH_2)_{1-3}NR^5(CH_2)_{1-3}$, $O(CH_2)_{2-6}NR^5$, $O(CH_2)_{2-3}NR^5(CH_2)_{1-3}$, $(CH_2)_{1-3}NR^5(CH_2)_{2-3}O$, $NR^5(CH_2)_{2-6}O$, $NR^5(CH_2)_{2-3}O(CH_2)_{1-3}$;

one of R^2 and R^3 represents a halogen, cyano, nitro, amino, hydroxyl, or a group selected from (i) C_1-C_6 alkyl optionally substituted by at least one C_3-C_6 cycloalkyl, (ii) C_3-C_8 cycloalkyl, (iii) C_1-C_6 alkyloxy optionally substituted by at least one C_3-C_6 cycloalkyl, and (iv) C_3-C_8 cycloalkyloxy, each of these groups being optionally substituted by one or more fluorine atoms, and the other of R^2 and R^3 represents a hydrogen or halogen atom;

either R^4 represents a 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system containing one or two nitrogen atoms and optionally an oxygen atom, the heterocyclic ring system being optionally substituted by one or more substituents independently selected from fluorine atoms, hydroxyl, carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, $-NR^6R^7$, $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$,

or R^4 represents a 3- to 8-membered saturated carbocyclic ring system substituted by one or more substituents independently selected from $-NR^6R^7$, $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$, the ring system being optionally further substituted by one or more substituents independently selected from fluorine atoms, hydroxyl and C_1-C_6 alkyl;

r is 1, 2, 3, 4, 5 or 6;

R^5 represents a hydrogen atom or a C_1-C_6 alkyl or C_3-C_8 cycloalkyl group;

R^6 and R^7 each independently represent a hydrogen atom or a C_1-C_6 alkyl, C_2-C_6 hydroxyalkyl or C_3-C_8 cycloalkyl group, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring;

with the provisos that,

(a) when A represents C(O)NH and R^4 represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X is other than a bond, and

(b) when A represents C(O)NH and X represents a group $(CH_2)_{1-6}$ or $O(CH_2)_{1-6}$, then R^4 does not represent an unsubstituted imidazolyl, unsubstituted morpholinyl, unsubstituted piperidinyl or unsubstituted pyrrolidinyl group, and

(c) when A represents NHC(O) and R^4 represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X is other than a bond, and

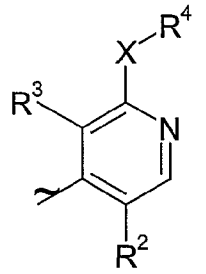
(d) when A represents NHC(O) and X represents $O(CH_2)_{1-6}$ or $NH(CH_2)_{1-6}$, then R^4 does not represent an unsubstituted 1-piperidinyl or unsubstituted 1-pyrrolidinyl group, and

(e) when A represents NHC(O) and X represents $O(CH_2)_{2-3}NH(CH_2)_2$, then R^4 does not represent an imidazolyl group;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein A represents NHC(O).

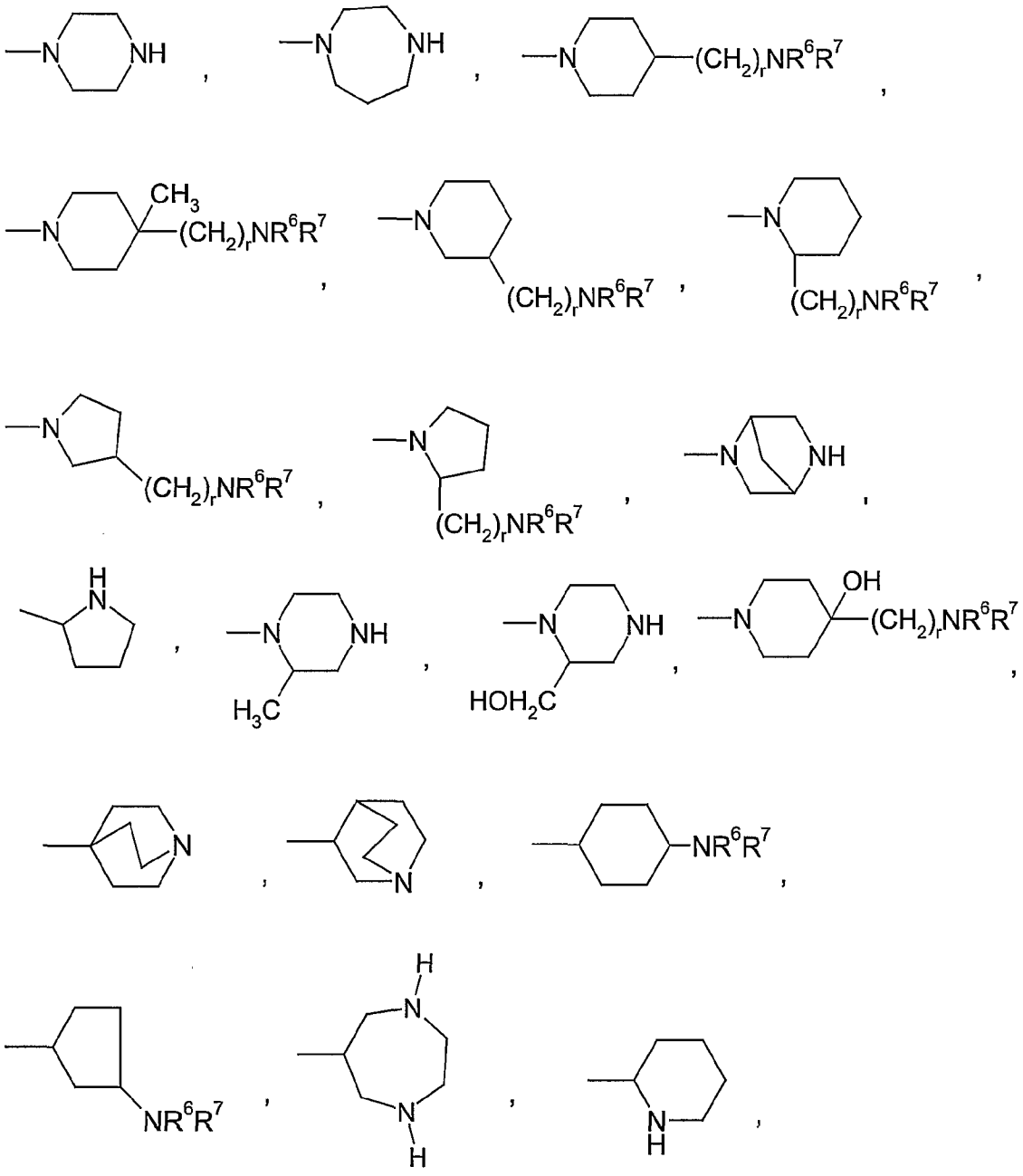
3. A compound according to claim 1 or claim 2, wherein Ar represents a group

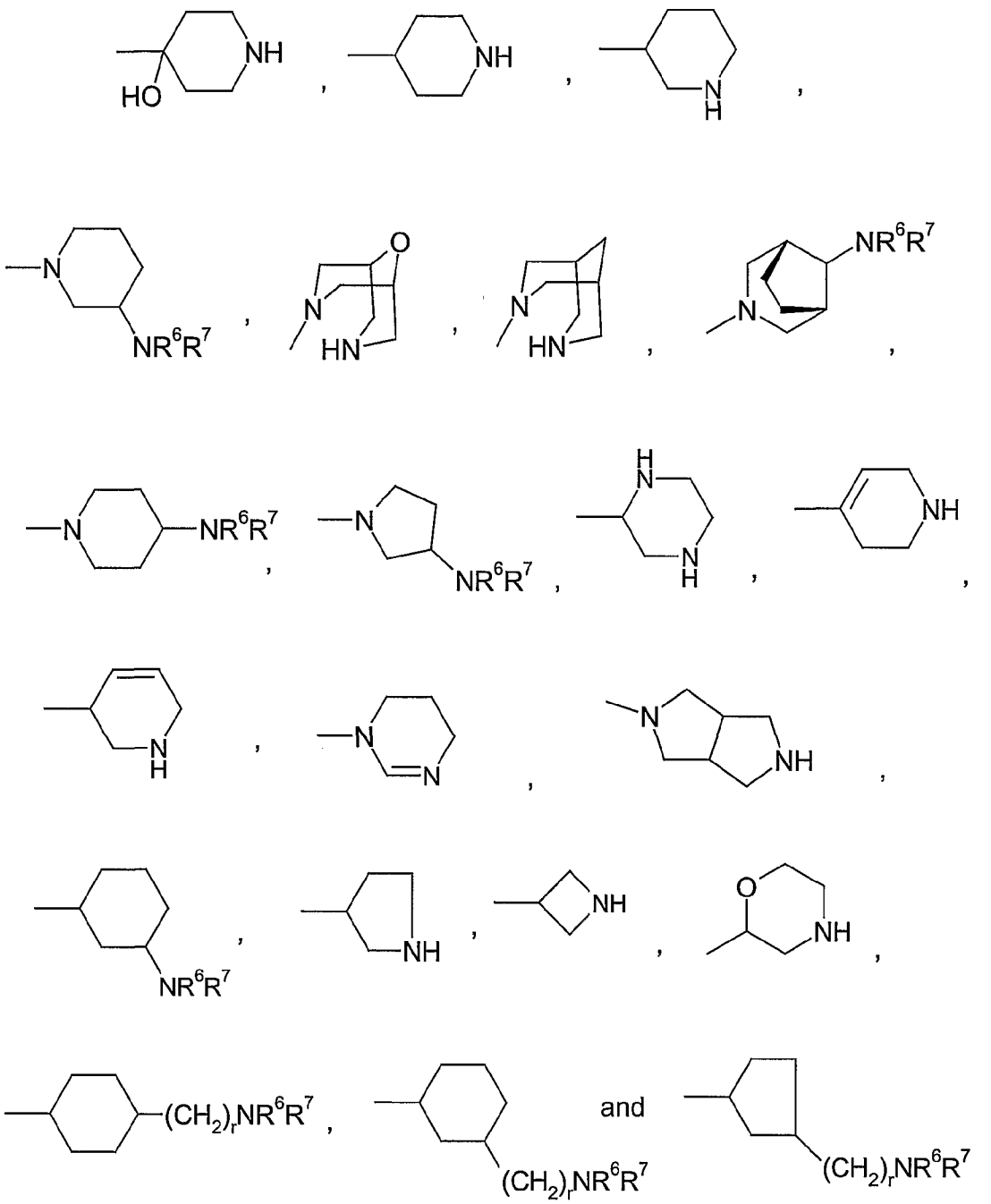


4. A compound according to any one of claims 1 to 3, wherein X represents a bond, an oxygen atom or a group $O(CH_2)_{1-6}$, NR^5 or $NR^5(CH_2)_{1-6}$.

5. A compound according to any one of claims 1 to 4, wherein R^4 represents a 3- to 9-membered saturated aliphatic heterocyclic ring system containing one or two nitrogen atoms and optionally an oxygen atom, the heterocyclic ring system being optionally substituted by one or two substituents independently selected from fluorine atoms, hydroxyl, carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, $-NR^6R^7$, $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$.

6. A compound according to any one of claims 1 to 4, wherein R^4 represents a group selected from:





7. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, according to claim 1 being:

5-Chloro-2-piperazinyl-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-([1,4]-diazepan-1-yl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(4-amino-piperidin-1-yl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(4-piperidinylmethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(4-piperidinylmethylamino)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(3-aminopyrrolidin-1-yl)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(4-piperidinylmethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

5-Chloro-2-(3-piperidinylmethoxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

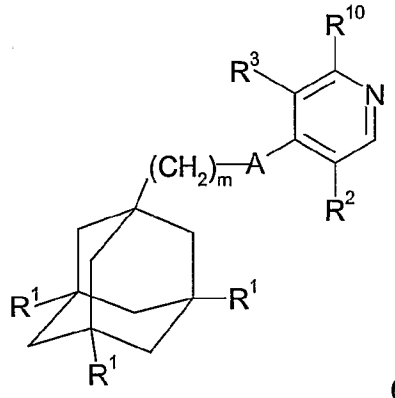
3-Chloro-2-piperazinyl-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt,

3-Chloro-2-(4-aminopiperidin-1-yl) -*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt, or

3-Chloro-2-(4-piperidinylmethylamino) -*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-pyridine-4-carboxamide, hydrochloride salt.

8. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises:

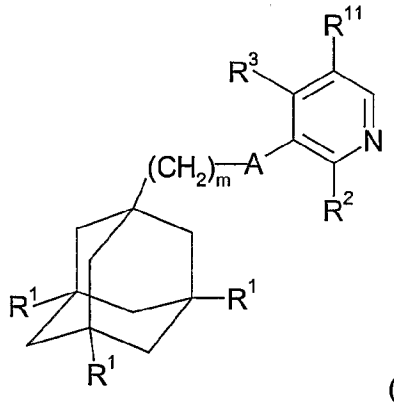
(i) when X represents an oxygen atom or a group $O(CH_2)_{1-6}$, $O(CH_2)_{2-6}O$, $O(CH_2)_{2-3}O(CH_2)_{1-3}$, $O(CH_2)_{2-6}NR^5$ or $O(CH_2)_{2-3}NR^5(CH_2)_{1-3}$, reacting a compound of general formula



(II)

wherein R^{10} represents a leaving group and m, A, R^1, R^2 and R^3 are as defined in formula (I), or

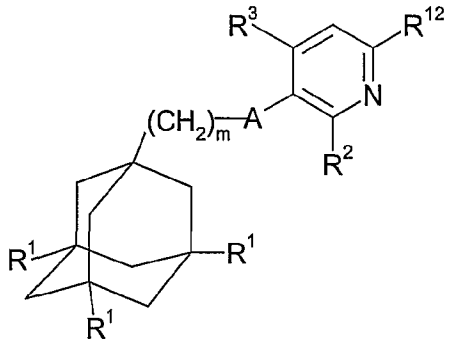
a compound of general formula



(III)

wherein R^{11} represents a leaving group and m, A, R^1, R^2 and R^3 are as defined in formula (I), or

a compound of general formula



(IV)

wherein R^{12} represents a leaving group and m, A, R^1, R^2 and R^3 are as defined in formula (I),

with a compound of general formula

$$R^4 - Y - OH \quad (V)$$

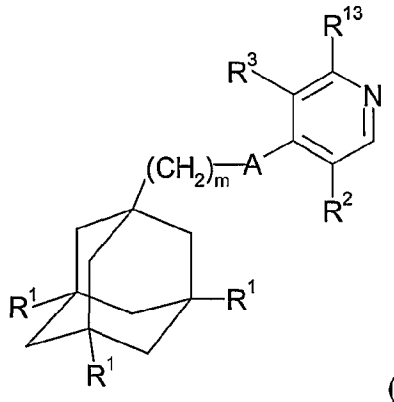
wherein Y represents a bond or a group $(CH_2)_{1-6}$, $O(CH_2)_{2-6}$, $(CH_2)_{1-3}O(CH_2)_{2-3}$, $NR^5(CH_2)_{2-6}$ or $(CH_2)_{1-3}NR^5(CH_2)_{2-3}$ and R^4 is as defined in formula (I), in the presence of a base or in the presence of a combination of a palladium catalyst, a phospine ligand and a base; or

(ii) when X represents a bond or a group NR^5, $NR^5(CH_2)_{1-6}$, $NR^5(CH_2)_{2-6}O$ or $NR^5(CH_2)_{2-3}O(CH_2)_{1-3}$, reacting a compound of formula (II), (III) or (IV) as defined in (i) above, with a compound of general formula

$$R^4 - Z \quad (VI)$$

wherein Z represents a hydrogen atom or a group NHR^5, $(CH_2)_{1-6}NHR^5$, $O(CH_2)_{2-6}NHR^5$ or a group $(CH_2)_{1-3}O(CH_2)_{2-3}NHR^5$ and R^4 and R^5 are as defined in formula (I), optionally in the presence of a palladium catalyst, a phosphine ligand and a base; or

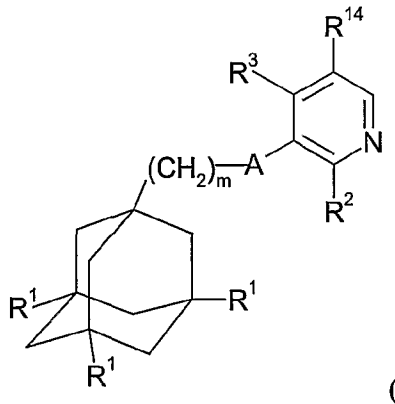
(iii) when X represents a CH_2 group, R^4 represents an optionally substituted 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system as defined in formula (I) and R^4 is linked to X through a nitrogen atom, reacting a compound of general formula



(VII)

wherein R^{13} represents a group $-CH_2L^1$, L^1 represents a leaving group and m, A, R^1, R^2 and R^3 are as defined in formula (I), or

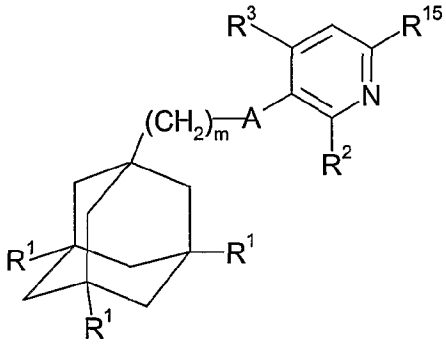
a compound of general formula



(VIII)

wherein R^{14} represents a group $-CH_2L^2$, L^2 represents a leaving group and m, A, R^1, R^2 and R^3 are as defined in formula (I), or

a compound of general formula



(IX)

wherein R^{15} represents a group $-CH_2L^3$, L^3 represents a leaving group and m, A, R^1, R^2 and R^3 are as defined in formula (I),

with a compound of general formula

$$R^{4'} - H \qquad (X)$$

wherein $R^{4'}$ represents an optionally substituted 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system as defined in R^4 in formula (I), in the presence of a base; or

(iv) when X represents a group CH_2O, reacting a compound of formula (VII), (VIII) or (IX) as defined in (iii) above with a compound of formula (V) as defined in (i) above wherein Y represents a bond, in the presence of a base or in the presence of a metal salt; or

(v) when X represents a group CH_2NR^5, reacting a compound of formula (VII), (VIII) or (IX) as defined in (iii) above with a compound of formula (VI) as defined in (ii) above wherein Z represents a group NHR^5; or

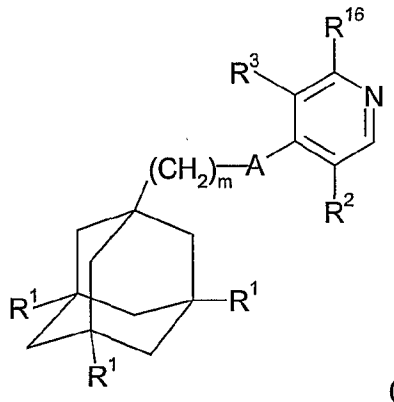
(vi) when X represents a group CH=, reacting a compound of formula (VII), (VIII) or (IX) as defined in (iii) above with trimethyl phophite and then with a compound of general formula (XI), $R^4 = O$, wherein R^4 is as defined in formula (I), in the presence of a base; or

(vii) when X represents a group $(CH_2)_{2-6}$, reacting a compound of formula (VII), (VIII) or (IX) as defined in (iii) above with trimethylphosphite and then with either a compound of general formula (XII), R^4CHO, wherein R^4 is as defined in formula (I) or with a compound of general formula (XIII), $R^4(CH_2)_{1-4}CHO$, in which R^4 is as defined in formula (I), in the presence of a base, followed by a hydrogenation reaction; or

(viii) when X represents a group $(CH_2)_{2-6}O$, reacting a compound of formula (VII), (VIII) or (IX) as defined in (iii) above with trimethylphosphite and then with a compound of general formula (XIV), $R^4O(CH_2)_{1-4}CHO$, in which R^4 is as defined in formula (I), in the presence of a base, followed by a hydrogenation reaction; or

(ix) when X represents a group $(CH_2)_{2-6}NR^5$, reacting a compound of formula (VII), (VIII) or (IX) as defined in (iii) above with trimethylphosphite and then with a compound of general formula (XV), $R^4NR^5(CH_2)_{1-4}CHO$, in which R^4 and R^5 are as defined in formula (I), in the presence of a base, followed by a hydrogenation reaction; or

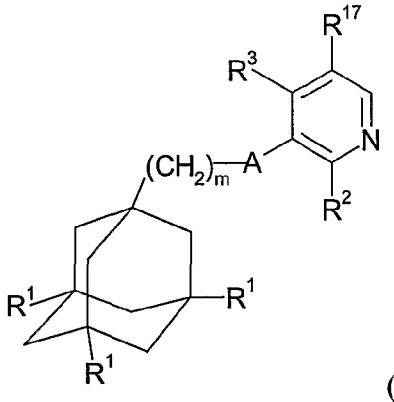
(x) when X represents a group $(CH_2)_{1-3}O(CH_2)_{1-3}$ or $(CH_2)_{1-3}O(CH_2)_{2-3}O$, reacting a compound of general formula



(XVI)

wherein R^{16} represents a group $-(CH_2)_{1-3}L^4$, L^4 represents a leaving group and m, A, R^1, R^2 and R^3 are as defined in formula (I), or

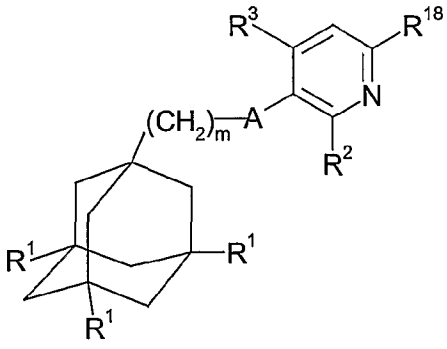
a compound of general formula



(XVII)

wherein R^{17} represents a group $-(CH_2)_{1-3}L^5$, L^5 represents a leaving group and m, A, R^1, R^2 and R^3 are as defined in formula (I), or

a compound of general formula



(XVIII)

wherein R^{18} represents a group $-(CH_2)_{1-3}L^6$, L^6 represents a leaving group and m, A, R^1, R^2 and R^3 are as defined in formula (I),

with a compound of formula (V) as defined in (i) above wherein Y represents a group $(CH_2)_{1-3}$ or $O(CH_2)_{2-3}$, in the presence of a base; or

(xi) when X represents a group $(CH_2)_{1-3}NR^5(CH_2)_{1-3}$ or $(CH_2)_{1-3}NR^5(CH_2)_{2-3}O$ reacting a compound of formula (XVI), (XVII) or (XVIII) as defined in (x) above with a compound of formula (VI) as defined in (ii) above wherein Z represents a group $(CH_2)_{1-3}NHR^5$ or $O(CH_2)_{2-3}NHR^5$;

and optionally after (i), (ii), (iii), (iv), (v), (vi), (vii), (viii), (ix), (x) or (xi) converting the compound of formula (I) to a further compound of formula (I) and, if desired, forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

9. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A process for the preparation of a pharmaceutical composition as claimed in claim 9 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 7 with a pharmaceutically acceptable adjuvant, diluent or carrier.

11. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 for use in therapy.

12. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.

13. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in the treatment of an obstructive airways disease.

14. Use according to claim 13, wherein the obstructive airways disease is asthma or chronic obstructive pulmonary disease.

15. A method of treating rheumatoid arthritis which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7.

16. A method of treating an obstructive airways disease which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01257

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/04, C07D 401/12, C07D 213/81, C07D 213/72, A61K 31/4427, A61K 31/496, A61K 31/551, A61P 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9929660 A1 (ASTRA PHARMACEUTICALS LTD), 17 June 1997 (17.06.97), the claims, example 27 --	1-16
X	WO 9929661 A1 (ASTRA PHARMACEUTICALS LTD), 17 June 1999 (17.06.99), the claims, examples 33 and 36 --	1-16
A	US 3464998 A (CARL PETER KRIMMEL), 2 Sept 1969 (02.09.69) -- --------	1-16

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2001	16 -10- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/01

International application No.
PCT/SE 01/01257

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9929660 A1	17/06/97	AU 1791499 A	28/06/99
		BR 9813368 A	03/10/00
		CN 1280560 T	17/01/01
		EE 200000320 A	15/08/01
		EP 1036058 A	20/09/00
		HU 0100431 A	30/07/01
		NO 20002785 A	01/08/00
		PL 340890 A	12/03/01
		SE 9704545 D	00/00/00
		SK 8412000 A	07/11/00
		TR 200001558 T	00/00/00
		US 6242470 B	05/06/01
WO 9929661 A1	17/06/99	AU 1791399 A	28/06/99
		BR 9813390 A	03/10/00
		CN 1284057 T	14/02/01
		EP 1036059 A	20/09/00
		HU 0004434 A	28/05/01
		NO 20002786 A	31/07/00
		PL 340906 A	12/03/01
		SE 9704544 D	00/00/00
		SK 8432000 A	11/12/00
		TR 200001605 T	00/00/00
		US 6201024 B	13/03/01
		US 6258838 B	10/07/01
		US 2001003121 A	07/06/01
US 3464998 A	02/09/69	NONE	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01257

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15-16
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 15-16 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.